

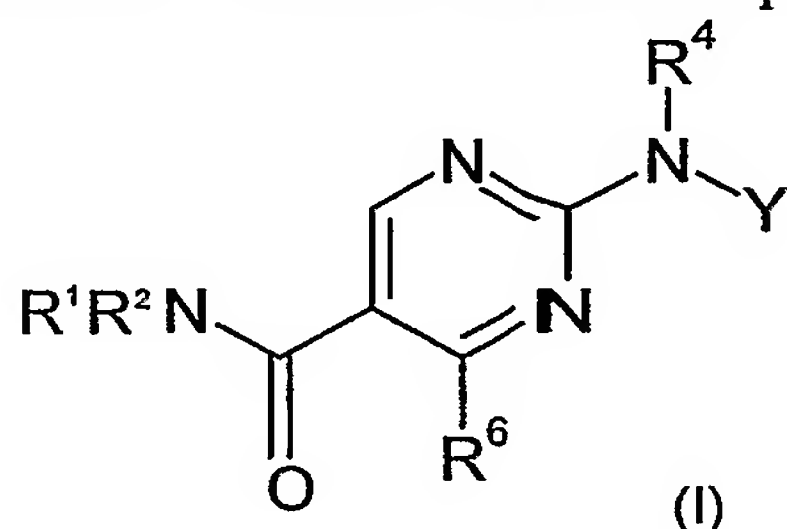
Claims

1. A method of treating a human or animal subject suffering from a condition which is mediated by the activity of CB2 receptors or a condition which is mediated by PDE4 which comprises administering to said subject a therapeutically effective combination of one or more CB2 modulators and one or more PDE4 inhibitors.

2. The use of a combination of one or more CB2 modulators and one or more PDE4 inhibitors in the treatment of a disease mediated by CB2 receptors or PDE4.

3. The use of a combination of one or more CB2 modulators and one or more PDE4 inhibitors in the manufacture of a medicament for treating a disease mediated by CB2 receptors or PDE4

4. The method according to claim 1 or the use according to claim 2 or claim 3, in which the CB2 modulator is selected from a compound of formula (I):



wherein

Y is phenyl, optionally substituted with one, two or three substituents;

R¹ is selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl and halosubstituted C₁₋₆ alkyl;

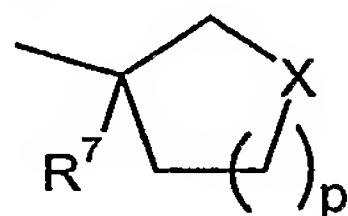
R² is (CH₂)_mR³ where m is 0 or 1;

or R¹ and R² together with N to which they are attached form an optionally substituted 4- to 8- membered non-aromatic heterocyclyl ring;

R³ is an optionally substituted 4- to 8- membered non-aromatic heterocyclyl group, an optionally substituted C₃₋₈ cycloalkyl group, an optionally substituted straight or branched C₁₋₁₀ alkyl, a C₅₋₇ cycloalkenyl or R⁵;

R⁴ is selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, or halosubstituted C₁₋₆ alkyl, COCH₃, and SO₂Me;

R⁵ is



wherein p is 0, 1 or 2 and X is CH₂, O, S, SO or SO₂;

R⁶ is methyl, chloro or CH_xF_n wherein n is 1, 2, or 3, x is 0, 1 or 2 and n and x add up to 3;

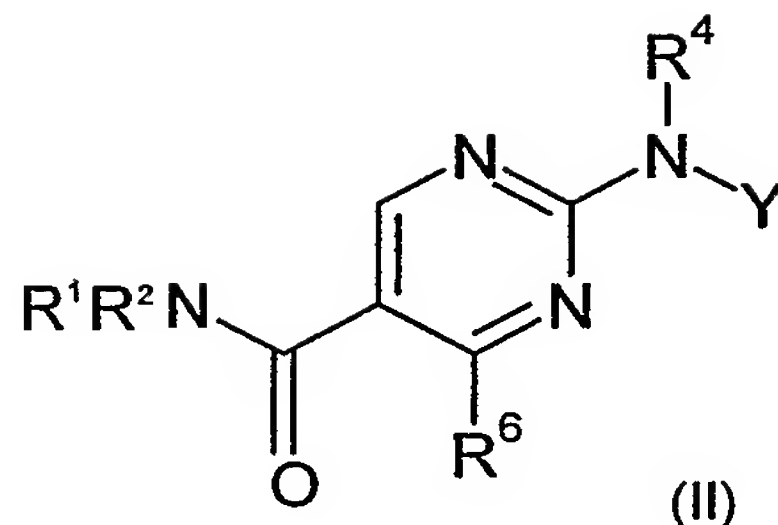
R⁷ is OH, C₁₋₆alkoxy, NR^{8a}R^{8b}, NHCOR⁹, NHSO₂R⁹, SO_qR⁹;

R^{8a} is H or C₁₋₆alkyl;

R^{8b} is H or C₁₋₆alkyl;

R^9 is C_{1-6} alkyl; and
 q is 0, 1 or 2;

or a compound of formula (II):



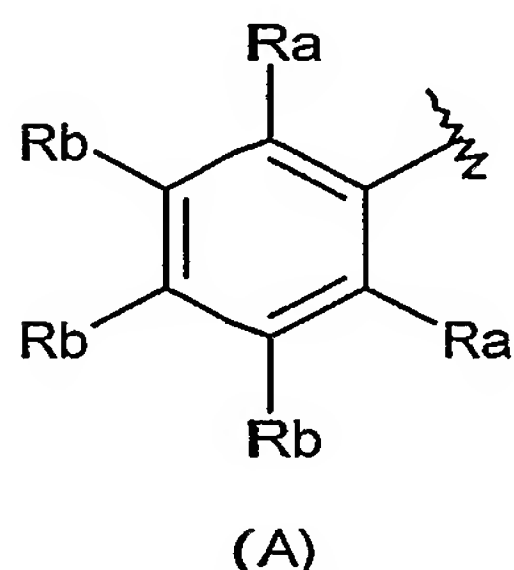
wherein

Y is phenyl, substituted with one, two or three substituents;

R^1 is selected from hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, and halosubstituted C_{1-6} alkyl;

R^2 is $C(R^7)_2R^3$;

R^3 is an optionally substituted 5- to 6- membered aromatic heterocyclyl group, or group A:



R^4 is selected from hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, and halosubstituted C_{1-6} alkyl, $COCH_3$, or SO_2Me ;

R^6 is methyl, chloro or CH_xF_n wherein n is 1, 2, or 3, x is 0, 1 or 2 and n and x add up to 3;

R_a can be independently selected from hydrogen, fluoro, chloro or trifluoromethyl;

R_b can be independently be selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, halo C_{1-6} alkoxy, hydroxy, cyano, halo, sulfonyl, $CONH_2$, $COOH$ or $NHCOOC_{1-6}$ alkyl; and

R^7 can be independently hydrogen or C_{1-6} alkyl,

with the proviso that the compound is not

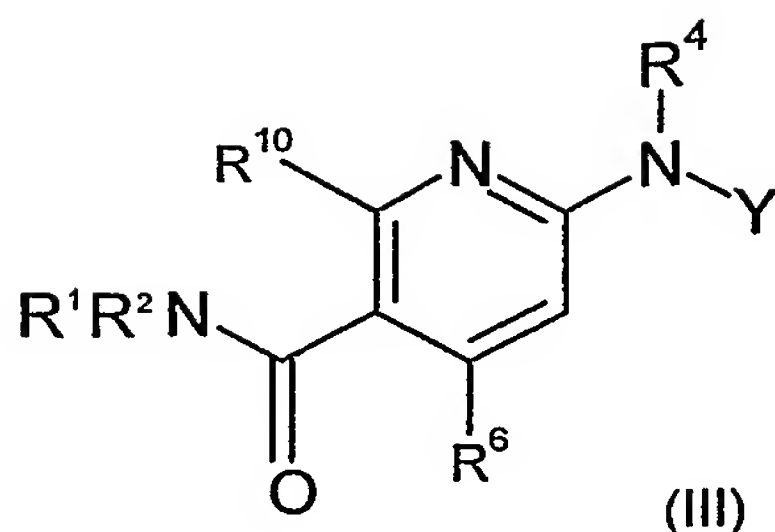
2-(4-*tert*-butyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid benzylamide;

2-(4-*tert*-butyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid benzyl-methyl-amide;

2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid 2-methoxy-benzylamide; or

2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid 2-bromo-benzylamide;

or a compound of formula (III):



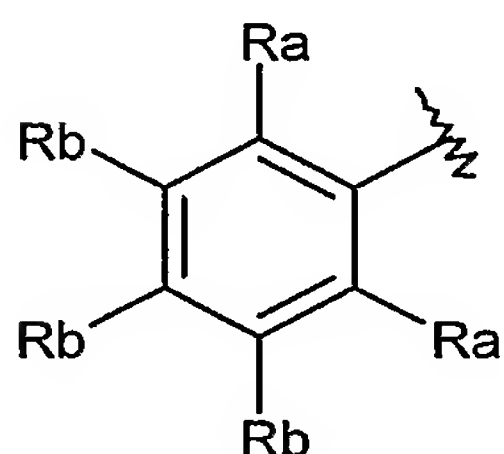
wherein

Y is phenyl, substituted with one, two or three substituents;

R¹ is selected from hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, or halosubstituted C₁₋₆ alkyl;

R² is (CH₂)_mR³;

R³ is an unsubstituted or substituted 5- to 6- membered aromatic heterocyclyl group, or group A:



(A)

R⁴ is selected from hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, or halosubstituted C₁₋₆ alkyl, COCH₃, and SO₂Me;

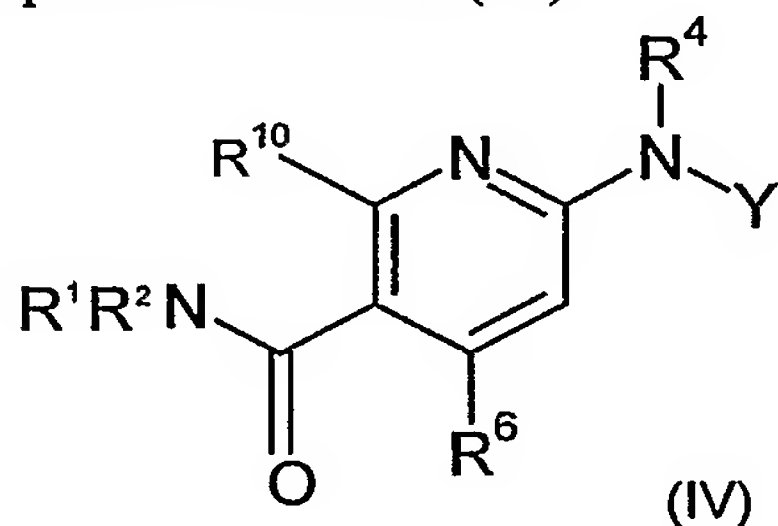
R⁶ is unsubstituted or substituted (C₁₋₆)alkyl or chloro and R¹⁰ is hydrogen or R¹⁰ is unsubstituted or substituted (C₁₋₆)alkyl or chloro and R⁶ is hydrogen;

Ra can be independently selected from hydrogen, fluoro, chloro or trifluoromethyl;

Rb can independently be selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo substituted C₁₋₆ alkoxy, hydroxy, cyano, halo, sulfonyl, CONH₂, COOH, SO₂CH₃, NHCOCH₃, NHSO₂CH₃ and CONHCH₃; and

m is 1 or 2;

or a compound of formula (IV):



wherein

Y is phenyl, unsubstituted or substituted with one, two or three substituents;

R¹ is selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, or halosubstituted C₁₋₆ alkyl;

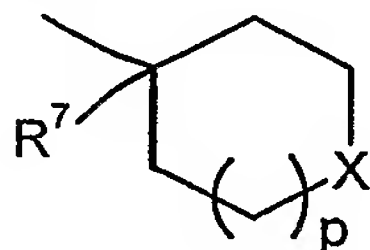
R² is (CH₂)_mR³ where m is 0 or 1;

or R^1 and R^2 together with N to which they are attached form an optionally substituted 4- to 8- membered non-aromatic heterocyclyl ring;

R^3 is a 4- to 8- membered non-aromatic heterocyclyl group, a C_{3-8} cycloalkyl group, a straight or branched C_{1-10} alkyl, a C_{2-10} alkenyl, a C_{3-8} cycloalkenyl, a C_{2-10} alkynyl, or a C_{3-8} cycloalkynyl any of which can be unsubstituted or substituted or R^5 ;

R^4 is selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, or halosubstituted C_{1-6} alkyl, $COCH_3$, or SO_2Me ;

R^5 is



wherein p is 0, 1 or 2, and X is CH_2 , O, or S;

R^6 is a substituted or unsubstituted (C_{1-6})alkyl or chloro and R^{10} is hydrogen or R^{10} is a substituted or unsubstituted (C_{1-6})alkyl or chloro and R^6 is hydrogen;

R^7 is OH, C_{1-6} alkoxy, $NR^{8a}R^{8b}$, $NHCO R^9$, $NHSO_2R^9$ or SO_qR^9 ;

R^{8a} is H or C_{1-6} alkyl;

R^{8b} is H or C_{1-6} alkyl;

R^9 is C_{1-6} alkyl; and

q is 0, 1 or 2;

or a pharmaceutically acceptable derivative thereof.

5. A method according to claim 1 or the use according to claim 2 or claim 3 in which the PDE4 inhibitor is selected from cilomilast, AWD-12-281, NCS-613, D-4418, CI-1018, V-11294A, roflumilast or T-4401, and pharmaceutically acceptable derivatives thereof.

6. The method of claim 1 or the use of claim 2 or claim 3 wherein the condition is an immune disorder, an inflammatory disorder, pain, rheumatoid arthritis, multiple sclerosis, osteoarthritis, osteoporosis, lung disorders, for example asthma, bronchitis, emphysema, allergic rhinitis, respiratory distress syndrome, pigeon fancier's disease, farmer's lung, chronic obstructive pulmonary disease, (COPD) and cough, or a disorder which can be treated with a bronchodilator.

7. A pharmaceutical composition comprising one or more CB2 modulators and one or more PDE4 inhibitors adapted for use in human or veterinary medicine.